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SUPREME COURT, U.S.

IN THE

Supreme Court of the United States

ALPHAPHARM PTY., LTD. and GENPHARM, INC.,

Petitioners,

v.

TAKEDA CHEMICAL INDUSTRIES, LTD. and TAKEDA PHARMACEUTICALS NORTH AMERICA, INC.,

Respondents.

ON PETITION FOR A WRIT OF CERTIORARI TO THE UNITED STATES COURT OF APPEALS FOR THE FEDERAL CIRCUIT

REPLY BRIEF

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CORPORATE DISCLOSURE STATEMENT

Petitioners' corporate disclosure statement was set forth at page *iv* of the Petition for a Writ of Certiorari. There are no amendments to that statement.

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REPLY ARGUMENT

I. The Evidence of Obviousness Could Not Be Fairly Evaluated as a Result of the "Teaching, Suggestion, or Motivation" Test

Takeda maintains that the Federal Circuit did nothing more than affirm the "all the evidence" approach recommended in *Graham v. John Deere Co.*, 383 U.S. 1 (1966). But the Federal Circuit panel did anything but apply either § 103 or *Graham*. Neither the statute nor *Graham* requires the patent challenger to show specific motivation to select the closest prior art. That the Federal Circuit cited § 103, *Graham*, and *KSR International Co. v. Teleflex, Inc.*, 127 S. Ct. 1727 (2007) is of little warrant. What matters is how the lower courts applied these decisions. *See, e.g., Freedman Seating Co. v. Am. Seating Co.*, 420 F.3d 1350, 1363 (Fed. Cir. 2005) (reversing judgment of nonobviousness where *Graham* cited but differences over the prior art insufficient to warrant a patent grant); *Jones v. Hardy*, 727 F.2d 1524, 1529 (Fed. Cir. 1984) (noting "*Graham*, supra, was cited but its guidance was not applied").

A. Both Lower Courts Would Only Accept Obviousness if the Closest Prior Art Were the Best Candidate to Select

The Federal Circuit panel squeezed Alphapharm through a standard no patent challenger could meet: specific motivation that the closest prior art "would be the *best* candidate [to select] as the lead compound"

(A16)[1] and motivation to modify that best compound in exactly the manner claimed (A11). These are not factual inquiries under *Graham*, as Takeda asserts. (Opp. 10.) Instead, they are artificial legal hurdles. What led this Court to grant certiorari in *KSR* was dismissal of common sense in favor of "principal reliance on the TSM test." *KSR*, 127 S. Ct. at 1738. This Court confronts the same problem.

Takeda asserts that under *KSR* all patent challengers must prove both what starting point the skilled person would have selected ("lead compound"), *and* prove motivation to modify the compound in such a way as to reach the claimed invention. (Opp. 14.) Absent those proofs, so the argument goes, a challenger engages in impermissible hindsight. Takeda's interpretation of *Graham* and *KSR* is misplaced. This Court's *Graham* factors must look with a kind of hindsight—knowledge of the patent—to determine the scope of the prior art *and* determine any difference between the prior art and the claimed invention. *See* 35 U.S.C. § 103 (requiring factfinder to assess "the differences between the subject matter sought to be patented and the prior art"). That difference requires a determination of the closest prior art, and—starting there—whether the skilled person would arrive at the claimed invention. This differs from the improper hindsight of imparting to the skilled person the claimed subject matter and then hypothetically guiding her to a known end. *See, e.g., Monarch Knitting*

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[1] "A__" refers to the petition appendix to this Court. "SA__" refers to Alphapharm's Supplemental Appendix to this Court. "RA__" or "R-JA__" refer to the Unified Joint Appendix in Federal Circuit No. 06-1329.

Mach. Corp. v. Sulzer Morat GmbH, 139 F.3d 877, 881 (Fed. Cir. 1998) ("[d]efining the problem in terms of its solution reveals improper hindsight in the selection of the prior art relevant to obviousness").

B. Takeda Attempts to Mask the District Court's Errors of Law as Nonreviewable Issues of Fact

Attempting to avoid addressing the improper legal hurdles placed before Alphapharm, Takeda tries to switch the subject. Takeda transforms each legal error into an unreviewable issue of fact, such as the district court's finding of "teaching away," the examiner's issuance of U.S. Patent No. 4,687,777 ("the '777 patent") despite compound b, and alleged admissions by Alphapharm of "hindsight." But the district court's legal errors infected each of these findings and prevented it from applying this Court's test of obviousness. All obviousness cases are fact-intensive. That reality does not cut off appellate review. Indeed, this Court extensively discussed the facts and analyzed the prior art in reversing the Federal Circuit's determination of nonobviousness in *KSR*. *See KSR*, 127 S. Ct. at 1735-38, 1743-45.

1. There Was No Teaching Away from Compound b

First, Takeda asserts that the prior art specifically "singled out" compound b as a non-starter. (Opp. 29.) This contention is meritless. The prior art taken as a whole taught to the contrary. Years after Sohda II noted the minor side effects of weight gain and brown fat in the highly effective compound b, Takeda declared it to

be "especially" "important" to the Patent Office. (SA24.) Takeda did so to secure allowance of U.S. Patent 4,444,779 ("the '779 patent") that not only covered compound b, but all the ethylated pyridyls Takeda was researching, including pioglitazone. (SA9-19.) While pioglitazone was not specifically disclosed, Takeda drew genus claims to cover all research on ethylated pyridyls. (SA19.) Far from being a "non-starter," Takeda specifically claimed compound b in the '779 patent. (SA19, claim 4.)

Prior art teaches away only when the reference demonstrates that the compound was "'unlikely to be productive of the result sought.'" *Medichem, S.A. v. Rolabo, S.L.*, 437 F.3d 1157, 1165 (Fed. Cir. 2006) (citation omitted). That could not be true of compound b. Takeda could not have otherwise obtained a claim covering the compound. (SA19.)

2. The Examiner of the '777 Patent Never Saw Takeda's Statements in the '779 Patent

Second, Takeda emphasizes the '777 patent examiner's review of the claimed compounds in light of compound b. (Opp. 7.) But Takeda was careful *not* to put the '779 patent or its file history before the examiner. (RA856-60.) The district court gave Takeda's failure to do so no weight, even though the genus claims of the '779 patent actually covered pioglitazone, and compound b was declared therein to be important. (A111-12.) Any claim that the examiner's issuance supports nonobviousness, is "much diminished" from the clear and convincing standard upon which the Federal Circuit based its affirmance (A27). *KSR*, 127 S. Ct. at 1745.

3. The District Court Erroneously Found and Improperly Weighted "Hindsight" in the Analysis

Finally, Takeda urges that Alphapharm admittedly engaged in "impermissible hindsight." (Opp. 21.) No such admission exists.[2] Rather, Alphapharm determined that the skilled artisan would look carefully at compound b because of its high efficacy and attempt to ameliorate its minor effects by substituting other groups on the pyridyl ring, such as methyl and ethyl. (RA2230, 192:21-22.) Indeed, Alphapharm's expert at trial noted that Takeda taught as much in the '779 patent. (SA112-17.) This too was dismissed as "hindsight" by the district court (A113), and affirmed on appeal.

But hindsight—inevitable in any backward-looking analysis—is not a substitute for the correct obviousness analysis. Rather than focusing on where the prior art might lead the skilled artisan, this Court noted that the obviousness analysis begins with the claims of the invention. *KSR*, 127 S. Ct. at 1742. A reason to combine prior-art elements need only be "apparent" from the prior art after considering any inferences or creative steps that a person of ordinary skill in the art would have employed. *Id.* at 1741. As Takeda admits, hindsight does nothing more than capture "a helpful insight." (Opp. 13.)

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[2] The district court may not have spent the time required to analyze Dr. Rosenberg's testimony comprehensively. The district court confused Alphapharm's Dr. Howard Rosenberg with Mylan's trial expert, Dr. Michael Rosenberg, even drawing an adverse inference against Alphapharm based on that misidentification. (A118, n.64.) The district court admitted its error. (R-JA41, n.1.)

Such an "insight" cannot justify the rigid rule that ensured a finding of nonobviousness on this record, even if it were present. *Id.* at 1740.

II. Takeda Artificially Constricts the "Objective Reach of the Claim" Analysis

Under *KSR*, "neither the particular motivation nor the avowed purpose of the patentee controls" but rather "[w]hat matters is the objective reach of the claim." *Id.* at 1741-42. Takeda interprets "objective" to mean that the purpose of the patentee does not control. (Opp. 16-17.) In doing so, it ignores the remainder of the phrase "reach of the claim." The analysis begins there, not with motivation. Thus, in the very next sentence this Court concluded that obviousness can be shown where "there was an obvious solution encompassed by the patent's claims." *Id.* at 1742.

The Federal Circuit erred by narrowing its analysis, beginning with what might have led the skilled artisan to select the closest prior art, and further to what motivated the skilled artisan to modify that compound in the manner claimed. The analysis should have been much broader, starting with any possible solution conceived by, and within the skill of, the ordinary medicinal chemist that would have led to the invention. (Opp. 8-9.)

III. The Federal Circuit Failed to Apply an "Objective" Analysis as Required Under *KSR*

By focusing on the objective reach of the claim, this Court restored clarity to the law of obviousness. This Court removed unprincipled discretion, and replaced it with an analysis of "objective reach." *Id.* at 1741-42. Objectivity has much to recommend to the law of obviousness, and in particular, the law of structural obviousness because "when a species is patentable over a genus" "is less than clear." (A28, Dyk, J., concurring.)

In *In re Dillon*, 919 F.2d 688, 692 (Fed. Cir. 1990), the Federal Circuit announced that for structurally similar compounds a presumption of obviousness arises "where the prior art gives reason or motivation to make the claimed compositions." Motivation to make existed there even though the compounds had different utilities, i.e., tri-orthesters used for "prevent[ing] phase separation between fuel and alcohol" and the claimed tetra-orthoesters used for reducing particulate emissions in fuels. *Id.* at 691. In *In re Deuel*, 51 F.3d 1552, 1558 (Fed. Cir. 1995), the Federal Circuit recognized that if the structure was particularly close, as close as a homolog as here, a prima facie could be made—"a prior art compound may suggest its homologs because homologs often have similar properties." Takeda insists that the language from these cases is discretionary, allowing a court to accept or reject structural obviousness as it sees fit. (Opp. 15.) But on what principled basis? If a prima facie case was made in *Dillon*, it was certainly made on these facts. Greater similarity cannot exist between claims 1 and 5 and compound b. These claims cover a mere homolog. (SA7.)

This Court clarified the law making it easier for the Federal Circuit to bring about uniformity by refocusing the emphasis on the claims, rather than motivation. *KSR*, 127 S. Ct. at 1741-42; *see also Manildra Milling Corp. v. Ogilvie Mills, Inc.*, 76 F.3d 1178, 1181 (Fed. Cir. 1996) (noting that Congress's primary purpose in creating the Federal Circuit was to "bring about uniformity in the area of patent law"). Takeda's constrained interpretation of "objective reach of the claim" would undo much of that work.

IV. The Prior Art Informed the Skilled Artisan about the Expected Properties of the Claimed Compounds

Takeda argues that even where one applies *KSR*'s flexible obviousness analysis, the prior art here gave no "apparent reason" to modify the prior art to obtain the claimed compounds. (Opp. 14.) Takeda is wrong. Applying *KSR* specifically to a case of chemical obviousness, the question is whether the prior art gave the skilled person an apparent reason to make minor modifications to optimize, though not qualitatively change, the utility of the closest prior-art compound. *KSR* asks for an apparent reason to make such closely related compounds, but the reason need not be the same reason that motivated the inventors. *KSR*, 127 S. Ct. at 1741.[3] Nor must the apparent reason to modify active

[3] The district court committed reversible error by holding that the skilled person had to be motivated to "achiev[e] the goals that the inventor sought to accomplish." (A94.) In fact, merely an effective—hypolipidemic and hypoglycemic—compound was enough of a reason under *KSR* for the skilled person to make the very minor changes to the closest prior art to obtain the claimed compounds.

prior-art compounds be explicit. *Id.* (noting that the reason to modify need not "seek out precise teachings directed to the specific subject matter of the challenged claim").

But here Takeda supplied that apparent reason by explicitly telling the world that the very modified compounds that it eventually claimed in the '777 patent would yield useful antidiabetic compounds. (SA11.) Takeda publicly and unequivocally supplied another apparent reason, during prosecution of its earlier '779 patent to antidiabetic TZDs. The '779 patent generically claimed the same compounds that Takeda specifically claimed in the '777 patent, and to obtain the '779 patent Takeda asserted that:

> the substituents in this case, ***actually cover a relatively narrow and well-defined group of constituents.*** Moreover, there should [be] no reason in the instant case for the Examiner to doubt that ***the claimed compounds having the specified substituent would function as a hypolipidemic and hypyglycemic (sic) agent as specified*** in the instant disclosure.

(SA26–27) (emphasis added.) Thus, the skilled person had an express reason to modify the closest prior-art compound. There was definitely a reason—even if not the same as the inventor's purported reason of lowering toxicity—for the skilled person to make the claimed compounds: they would be useful antidiabetic agents. At the very least such modifications—which Takeda candidly insisted were a "narrow and well-defined" group—were obvious to try. Even the district court admitted as much. (A125-26.)

Takeda argues, as a last resort, that even if the prior art gave an apparent reason to modify compound b to obtain pioglitazone (with similar utility), that pioglitazone had unexpected results, and was thus patentable. (Opp. 29.) ***Unexpected results*** may rebut a case of prima facie structural obviousness. *Pfizer, Inc. v. Apotex, Inc.*, 480 F.3d 1348, 1371 (Fed. Cir.), *cert. denied*, 128 S. Ct. 110 (2007). But "[e]xpected beneficial results are evidence of obviousness of a claimed invention, just as unexpected beneficial results are evidence of unobviousness thereof." *In re Gershon*, 372 F.2d 535, 537 (C.C.P.A. 1967). Here, the results—hypolipidemia and hypoglycemia—were expected because Takeda had told everyone that this "narrow and well-defined group" would have such properties. (SA26-27.) And while toxicity for one of the claimed compounds was "improved," (*see infra* Part V) this was merely a matter of degree.[4] Superiority alone is insufficient. *See In re Adamson*, 275 F.2d 952 (C.C.P.A. 1960).

V. The Federal Circuit Precluded Key Evidence Refuting the Alleged Unexpected Results of the Claimed Compounds

Takeda asserts that the finding of unexpected results overcame "any prima facie case of obviousness," "independently support[ed] the judgment," and was "not even challenged by Alphapharm." (Opp. 12.) Takeda's assertion lacks merit. First, the district court denied

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[4] Takeda's citation to *In re Ruschig*, 343 F.2d 965, 978 (C.C.P.A. 1965) is inapposite. The prior-art compound there did not share the toxicity continuum with the claimed compound, as is the case here, but was ***lethal***.

Alphapharm the opportunity to rebut Takeda's alleged showing of unexpected results by excluding key scientific studies Takeda itself conducted. Second, Alphapharm challenged the district court's findings concerning unexpected results. (R-JA2350-55; R-JA2824-26.)

To demonstrate unexpected results, Takeda relied on toxicity tests where pioglitazone demonstrated a smaller increase in heart weight, liver weight, and reduction of red blood cells than compound b. During trial, the district court excluded two studies Alphapharm proffered demonstrating that there were no appreciable differences in toxicity results between pioglitazone and compound b. The first study was a 13-week oral toxicity study that found that pioglitazone caused significant increases in heart weights. (RA1642-731.) The second study, a 4-week study, noted that pioglitazone, and specifically its central and right-hand structures (structures that pioglitazone shared with compound b), increased heart weight. (RA1732-815.)

The evidence of unexpected results for the claims was weak, and therefore insufficient to rebut the prima facie case of obviousness. As discussed above, Judge Dyk noted that Takeda never rebutted the prima facie case concerning the remaining compounds with any such showing. (A28.) There is no bar to finding a secondary consideration wrongly decided by the court below. For example, in *Merck & Co. v. Teva Pharmaceuticals USA, Inc.*, 395 F.3d 1364, 1376 (Fed. Cir. 2005), the patentee claimed that the commercial success of its drug alendronate demonstrated nonobviousness. The Federal Circuit disagreed, and reversed the finding. *Id.* So too in *Syntex (U.S.A.) LLC v. Apotex, Inc.*, 407 F.3d 1371,

1379 (Fed. Cir. 2005), where the patentee relied on the unexpected properties of the claimed anti-inflammatory eye drops, but the Federal Circuit disagreed.

Takeda asserts that Alphapharm's alleged admissions constitute "conclusive evidence" to support its claims of unexpected results. (Opp. 33.) However, these admissions were based on early depositions concerning data provided to the Patent Office. The witnesses were not shown, nor were they apprised of the fact that Takeda later admitted that its presentation of the heart-weight and blood-cell count data concerning compound b and pioglitazone was erroneous. In any event, recognition of "superior" results does not show *unexpected results. In re Merck*, 800 F.2d 1091, 1099 (Fed. Cir. 1986) (noting that the evidence must show that the compounds differ "in such an appreciable degree that the difference was really unexpected.").

Should the Court reverse here with respect to the application of the TSM test, at the very least, the case should be remanded for additional findings on the issue of unexpected results.

CONCLUSION

Alphapharm respectfully requests that this Court grant the petition for a writ of certiorari, vacate the judgment of the Federal Circuit, and if necessary remand to the district court for a complete record on the issue of unexpected results.

Respectfully submitted,

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